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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/376,317	08/18/99	STOKES K	P-3569CON

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EXAMINER	
STROUP, C	
ART UNIT	**PAPER NUMBER**
1633	2

DATE MAILED: 05/12/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/376,317	Stokes et al
Examiner	**Group Art Unit**
Stroup, Carrie	1633

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-25 and 39-60* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-25 and 39-60* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's preliminary amendment has been entered. Claims 2, 3, and 26-38 have been canceled. Claims 1, 4-25, and 39-60 are currently pending in the present application.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 56-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's claimed invention is to a method of expressing conduction protein in cardiac tissue comprising delivering an expression vector comprising a nucleotide sequence encoding said conduction protein to said cardiac tissue using the disclosed catheter delivery system. The specification provides prophetic exemplifications for the isolation and purification of nucleic acid molecules encoding the connnexin proteins and insertion of connexin cDNA into plasmid and adenoviral vectors (pages 26-28). The specification also provides general guidelines on recombinant DNA production to include lists of potential promoters, the use of polyadenylation signals, incorporation by reference for the coding sequences for Cx40, Cx43, and Cx45, and potential doses for administration of adenoviral vectors.

The specification fails to provide an enabling disclosure for the use of a catheter delivery device for expressing any gene encoded within a vector, such as the claimed viral and adenoviral vector, within the cardiac tissue of any host. The specification fails to provide essential teachings on the method of delivering genetic material from said device in such a manner that any electrical energy generated by the device would not adversely impact the ability of the vectors to transduce the cells or damage the vector's stability and ability to express the encoded transgene. The specification also does not disclose to what extent administration of an electric field from the Applicants' device will have on the quantity of DNA delivered into the cells as a result of an increase in permeation of the cell membrane. It is well known within the art that the administration of an electric field, such as in the use of electroporation, can result in a significant level (e.g. 40-80%) of cell lysis (e.g. See Weaver et al, US Patent 5,019,034, col 3, lines 44-64). The specification also fails to disclose the manner and ability to transduce cardiac tissue cells which have been damaged due to the use of a helical electrode which is screwed into the myocardium.

The specification also fails to disclose the method of use of each of the claimed connexins, for example, the amount of pfu comprising each of the claimed connexin. Kanter et al disclose that Cx40, Cx43, and Cx45 are three different type of gap junctions with different biophysical properties, and that in combination they are believed to be important in the regulation of cellular coupling. However, they have regional differences in expression within the various cardiac tissues, such as the Purkinje fibers and ventricular myocytes, and they are not expressed in one-to-one-to-one ratios within any cardiac tissue (Kanter et al, pg 861, col 1-2; pg 866). It is noted, though, that the specification only provides the potential dose ranges for adenoviral vectors utilizing any or all of the connexins. The specification fails to disclose the specific level of expression required for each of the claimed connexins in the treatment of any specific cardiac disorder.

Furthermore, Applicant's are reminded that gene therapy is a highly unpredictable art largely because there are barriers to the *in vivo* delivery of DNA such as: " (1) the rapid degradation of DNA within tissues or blood by

nuclease; (ii) the limited dispersion of DNA from the site of interstitial administration; (iii) the inability of DNA to cross intact basement membranes of the endothelium or epithelium effectively; (iv) the rapid clearance of DNA from the vascular compartment by cells of the reticuloendothelial system; (v) the need for effective interaction with the surface of the target cell to induce internalization; (vi) destruction of DNA in the endosomal/lysosomal compartments by nuclease, acid and/or reducing agents; and (vii) the need to penetrate to the nucleus of cells across the periplasmic membrane and nuclear membrane.". (Ledley, pg 1603, col 1, para 3-col 2, para 1). The extent of these barriers directly affects the bioavailability and hence the required dose to effectively elicit any therapeutic response.

Additionally, an evaluation of the state-of-the-art of gene therapy by Verma and Somia in Nature 1997, vol 387, pages 239-242 concluded that " In principle, gene therapy is simple: putting corrective genetic material into cells alleviates the symptoms of disease. In practice, considerable obstacles have emerged.....But the problems- such as lack of efficient delivery systems, lack of sustained expression, and host immune response reactions- remain formidable challenges.....And Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is no single outcome that we can point to as a success story" (Abstract, & pg 239, col 1, para 1-2). Therefore, in light of the unpredictability in the art of gene therapy, and the failure of the specification to overcome said unpredictability by providing explicit teachings on the method of administering any connexin for the treatment of any specific cardiac disorder with or without the use of electrical energy, one of skill in the art would be required to practice undue experimentation to utilize the claimed invention to any therapeutic end.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 5, 10, 17-19, and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is unclear as to the meaning of "reservoir means comprises said interior with said supply of conduction protein genetic material therein". By the use of "comprising" is Applicant disclosing that the reservoir is in the interior of the helical element, or that is can supply genetic material to the interior?

Claim 10 is unclear as to the metes and bounds of "means of forcing" genetic material from the reservoir. Does this include mechanical, pressurized, osmotic, electro-magnetic, etc...force?

Claims 17-19 are unclear as to "genetic material is protein" versus "genetic material produces a protein". "Genetic" is an art accepted term referring to genes and that which comprises such, and therefore includes DNA and RNA. Proteins are the result of genetic material being properly processed via transcription and translation and thus are a separate entity from genetic material.

Claim 25 is unclear as to the metes and bounds of "a peelable introducer sheath". How is a rigid metal device "peelable"? What exact part on the device constitutes a "introducer sheath" and what is its mechanical or electrical function?

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1, 9-25, 39-55

6. Claims 1-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mulier et al (WO 95/05781) in view of Leiden et al (WO 94/11506) and Kanter et al (1994).

Applicant's claimed invention is to a delivery system for delivering genetic material, such as DNA or RNA encoding cardiac gap junction proteins Cx40, 43, or 45, , to cardiac tissue comprising a reservoir supplying .1-10ml of genetic material and a delivery means comprising a catheter with an opening at the distal end wherein said reservoir is located, a means to deliver genetic material from the reservoir to the catheter opening, mapping electrode at the distal end of the catheter, a conductor means for connecting said mapping electrode to the proximal end of said catheter, a hollow helical screw-in element loaded with a bolus of genetic material and ports for egress of genetic material into said cardiac tissue.

Muelier et al disclose a catheter device comprising a transvenous endocaridal catheter with a mapping electrode or pacing electrode at the distal end of the catheter (pg 3, lines 30-33; pg 5, lines 5-16), a reservoir and lumen for delivering Ringer's solution through the catheter by means of pressurized force if necessary (pg 7, line 31, Figure 6, #100) and to the surrounding tissue at a rate of 1cc/min, a hollow helical screw-in element with ports for egress of fluid (pg 6, lines 15-17; pg 1 Figure #26), an electrical generator coupled to the device at the proximal end and conducted to the distal end (Figure 6). Muelier et al does not teach the use of genetic material in place of the Ringer's solution.

Leiden et al disclose the use of catheters to deliver genetic material to cardiac tissu, such as adenoviral vectors encoding growth factor genes (Example 2, Claims 16-22).

Kanter et al disclose the presence of Cx40, Cx43, Cx45 in the human left ventricle and indicates that they may contribute to divergent mechanisms of regulation of cardiac conduction. (Abstract).

In light of Muelier, Leiden, and Kanter et al it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the Ringer's solution in the device disclosed by Muelier with a composition

comprising genetic material, such as vectors encoding Cx40, Cx43, and Cx45. One would have been motivated to do this to deliver therapeutic genetic agents through a catheter to cardiac tissue as disclosed by Leiden et al, wherein the genes express proteins that are known for facilitating electrical conduction of cardiac tissue by a device that also functions to map and pace, and utilizing a catheter device such as Muelier's et al so that both cardiac mapping or pacing could be conducted with gene therapy in one invasive procedure for the same cardiac disorder.

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carrie Stroup whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached at (703) 308-0447. The fax phone number for this Group is (703) 308-0294.

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